

INHIBITORY PROCESSING IN YOUNG REGULAR CANNABIS USERS: AN EVENT-RELATED POTENTIAL STUDY

Janette L. Smith, Philip J. Clare, Jaimi M. Iredale, Richard P. Mattick and Aneta
Dimoska Di Marco

Technical Report Number 67

Funded by a UNSW Vice-Chancellor's Postdoctoral Research
Fellowship to Dr Janette Smith

ISBN: 978-0-7334-3833-2

©NATIONAL DRUG AND ALCOHOL RESEARCH CENTRE,
UNIVERSITY OF NEW SOUTH WALES, SYDNEY, 2018

This work is copyright. You may download, display, print and reproduce this material in unaltered form only
(retaining this notice) for your personal, non-commercial use or use within your organisation.

All other rights are reserved. Requests and enquiries concerning reproduction and rights should be addressed to
the information manager, National Drug and Alcohol Research Centre, University of New South Wales, Sydney,
NSW 2052, Australia.

TABLE OF CONTENTS

TABLE OF CONTENTS	2
EXECUTIVE SUMMARY	3
1. INTRODUCTION	4
2. METHODS	5
2.1 Participants.....	5
2.2 Measures.....	5
2.3 Stop-signal task.....	5
2.4 Electrophysiological recording	6
2.5 Data analysis.....	6
2.6 Statistical analysis	7
3. RESULTS.....	7
3.1 Demographics and balance diagnostics	7
3.3 Behavioural performance	8
3.4 Event-related potential data	9
4. DISCUSSION.....	10
5. CONCLUSIONS.....	12
6. REFERENCES	14
ACKNOWLEDGEMENTS.....	17

EXECUTIVE SUMMARY

Aims: Dysfunction in inhibitory and error-evaluation systems has been highlighted in theories of the development and maintenance of addiction, but the evidence suggests the dysfunction differs by drug. Specifically, among cannabis users, the literature presents an inconsistent view of behavioural measures in support of such deficits; underlying alcohol use, which has also been linked with self-regulation problems, may explain these differences. We report a novel study examining inhibitory control in young regular cannabis users and extend on past research by controlling for alcohol use and including measurement of event-related potentials (ERPs).

Methods: 20 regular cannabis users and 74 non-users (aged 18-21 years) completed a stop-signal task while brain electrical activity was recorded. Post-experimentally, propensity weighting accounted for group differences in alcohol use. Measures include the time required to stop a response (stop-signal reaction time or SSRT), N2 and P3 amplitude and latency to stop-signals on which inhibition failed vs. was successful, and the error-related negativity and positivity (ERN and Pe, respectively) to erroneous responses.

Results: Cannabis users and non-users did not differ on SSRT, or reaction time or accuracy to Go-only trials. The groups also did not differ on ERN or Pe amplitude or latency, on N2 or P3 latency for successful or failed inhibitions, or on N2 or P3 amplitude to successful inhibitions. However, the cannabis user group displayed increased N2 amplitude, and decreased P3 amplitude, on failed inhibition trials, relative to non-users.

Discussion: Together, the results suggest intact inhibitory processing and error monitoring, but changes in conflict monitoring processes among young regular cannabis users. Limitations of the study are discussed, including the group differences in alcohol consumption, the heaviness of cannabis use, and the possibility of acute cannabis intoxication effects. Future research confirming conflict monitoring deficits among young cannabis users is indicated.

1. INTRODUCTION

Recent models of the development and maintenance of substance abuse implicate deficient inhibitory control over overt behaviours (Hester et al., 2010, Goldstein and Volkow, 2002), and indeed difficulties with controlling behaviour are implicated in DSM-5 criteria for substance abuse including repeated failed efforts to reduce use, and using more or more often than intended (American Psychiatric Association, 2013). Although an inhibitory deficit appears to be common across users of several categories of substances (Smith et al., 2014), for cannabis the evidence is mixed. In this study we focus on inhibition using the stop-signal paradigm (Logan et al., 1984), which requires participants to press a left or right hand button in response to a primary 'Go' stimulus (e.g., a leftward or rightward arrow), and inhibit that response when an occasional stop-signal (e.g., an auditory tone) is presented. The delay between the Go and stop-signal stimuli is varied to observe a participant's probability of inhibition at different delays. The result is an inhibition function from which one can estimate the time it takes the inhibitory process to stop a response, also known as the 'stop-signal reaction time' (SSRT). In healthy control adults, typical SSRT is around 200-250ms (Band et al., 2003); SSRT is significantly longer in users of cocaine, methamphetamine, and alcohol (Smith et al., 2014). However, despite some studies reporting significantly longer SSRT among cannabis users (Moreno et al., 2012), or with a medium-large effect size which approaches statistical significance (Lovell et al., 2018), the majority of studies report only small/non-significant differences in SSRT between cannabis users and their assorted control groups (Ramaekers et al., 2009, Theunissen et al., 2012, Jutras-Aswad et al., 2012, Huddy et al., 2013, Grant et al., 2012, Filbey and Yezhuvath, 2013).

Apart from variations between studies in the extent of participants' cannabis use, a possible factor underlying the inconsistent evidence for an inhibitory deficit may be the extent of alcohol use in participants; heavy drinking is itself associated with a small inhibitory deficit (Smith et al., 2014). Since the majority of cannabis users also drink alcohol (Australian Institute of Health and Welfare, 2011), it is important to assess and control for the level of alcohol consumption in both cannabis-using and non-using control groups. In this study, we will improve on prior research into possible inhibitory deficits associated with recreational cannabis use by taking into account the confounding effects of alcohol use.

We included both behavioural and brain functional measures of response inhibition to examine this effect. Specifically, we measured event-related potentials (ERPs), the brain's average electrical response to an event, measured non-invasively from the scalp. Brain functional measures can be more sensitive to deficits than behavioural measures alone (Mahmood et al., 2013, Tarter et al., 2003, Norman et al., 2011, Luijten et al., 2016), and because characteristic peaks and troughs of the ERP waveform have been linked with specific stages of processing, ERPs can highlight which processes differ or are intact. In contrast, behavioural measures such as accuracy or reaction time index only the final outcome of the processing stream. The ERP components most commonly examined in response to stop-signal stimuli are the N2 and P3 components, compared on trials where inhibition was successful (i.e., no response was made) and when inhibition fails to stop the response. The N2 is a negative-going component peaking 150-300ms post-stop-signal, while the P3 is a positive-going component peaking around 250-400ms post-stop-signal. The N2 is typically larger on failed inhibition trials, and thus is thought to represent error-related activity (Dimoska et al., 2006) or response conflict monitoring (Kok et al., 2004); the P3 is typically larger on successful inhibition trials, and thus is thought to represent the active cancellation of the motor response (Kok et al., 2004). ERPs are also examined time-locked to responses, with a difference wave calculated for erroneous responses (i.e., trials where inhibition failed) versus correct responses (i.e., on Go trials for which no stop-signal is delivered). ERP components examined include the error-related negativity (ERN) and error positivity (Pe). The ERN typically peaks in the first 100ms after an error, and indexes unconscious error detection, while the Pe is a slow wave occurring around 300-500ms post-error and indexes conscious error detection (Falkenstein et al., 1990, Falkenstein et al., 2000, Nieuwenhuis et al., 2001, Simons, 2010).

Only one study (Theunissen et al., 2012) has examined ERPs in the stop-signal task in 12 heavy cannabis users (smoking more than four times per week) vs. 12 occasional cannabis users (once a week or less; the minimum use was not specified). Groups were matched for tobacco and alcohol use, as well as duration and heaviness of cannabis use (that is, they differed on frequency of use only). The researchers found no group differences in the amplitude of N2 to stop-signals on successful inhibition trials, or to Go signals; they did not measure N2 on failed inhibition trials, nor any other ERP component.

In the current study, we extend the literature by not only reporting data from a larger sample, but with careful statistical approaches accounting for differences in alcohol use, and with a greater range of ERP components measured, indexing a wider range of psychological processes.

2. METHODS

2.1 Participants

Participants were 94 young adults (aged 18-21 years) recruited from the University of New South Wales. They were recruited into two groups: Cannabis Users (9 female, 11 male) who reported using cannabis at least twice per month for at least the last 12 months, and Controls (33 female, 41 male) who reported using cannabis less often than this (including never). Cannabis Users were mostly also heavy drinkers (85% consumed 4 or more standard drinks at least once a month); data from non-cannabis-using Controls (reported in Smith et al., 2016) also varied on their lifetime alcohol consumption, such that 50% reported episodic heavy drinking. Participants were recruited from posters displayed on the university campus, via an online paid research participation system, and via participant referral. They were excluded if they had ever had an epileptic seizure, a serious head injury or period of unconsciousness, uncorrected hearing or vision problems, or regular (twice a month) use of other drugs except tobacco (including illicit drugs, and prescription drugs used outside the reason or dose for which they were prescribed). Additionally, participants reported no use of psychoactive medication. All participants gave written informed consent, and the UNSW Human Research Ethics Committee approved the protocol before data collection began. Participants completed a single 2 hour laboratory session, and were thanked for their time and effort with a \$20 iTunes voucher and \$10 cash.

2.2 Measures

Participants completed a brief demographic questionnaire, followed by the Alcohol Use Disorders Identification Test (Saunders et al., 1993). The third question of the AUDIT was changed to “How often do you have four or more standard drinks?” to reflect Australian alcohol consumption guidelines (National Health and Medical Research Council, 2009). Participants next completed the Drug Use Disorders Identification Test – Extended (DUDIT-E, Berman et al., 2007), which assesses the frequency of use of a range of drug classes other than alcohol; tobacco use is assessed but does not contribute to the total score. The reported frequency of cannabis use was used to group participants. Participants then underwent structured interviews assessing lifetime alcohol use and lifetime cannabis use using modified versions of the Lifetime Drinking History interview (Skinner, 1977). This records the frequency and quantity of consumption in relatively homogenous phases from the onset of regular drinking (one standard drink per month) or regular cannabis use (one use occasion per month), and can be used to estimate the number of standard drinks consumed in the participant’s lifetime, the age of first regular use of cannabis, and the frequency of cannabis use in the last 6 months. Participants were required to reference a standard drinks guide while they completed the AUDIT and the alcohol lifetime history.

2.3 Stop-signal task

The stop-signal task used has been described previously in Smith et al. (2016). Go stimuli were green leftward and rightward arrows appearing above a grey central fixation cross on a

black background. Go stimuli were presented for 1000ms with a mean SOA of 1500ms (1200-1800ms). Participants were instructed to press the 'S' or 'L' button on a standard QWERTY keyboard with their left or right index finger, respectively, according to the direction of the arrow. On a random 25% of trials, a 1500Hz pure tone lasting 200ms with 20ms rise and fall time was presented binaurally through headphones; this stop-signal indicated to participants that they must inhibit their response. Participants completed a 10 trial practice block with only Go signals, followed by a 40 trial practice block with 10 stop-signal trials set at post-Go-stimulus delays of 100ms, 200ms, 300ms, 400ms and 500ms (2 at each delay). Participants then completed 4 experimental blocks of 120 trials each. Mean reaction time (MRT) to the Go stimulus on trials where no stop-signal was presented was calculated for the second practice block and first three experimental blocks, and used to set delays in the subsequent block. In the experimental blocks, stop-signals were delivered at set intervals before MRT from the previous block (MRT-450, MRT-350, MRT-250, MRT-150, and MRT-50ms) (Logan et al., 1984, Logan, 1994). This method counteracts strategic slowing (i.e., slowing of Go responses in order to increase the probability of successful inhibition) by delaying stop-signals by an equivalent amount in the following block, so that the probability of inhibition is relatively constant over blocks. Where the MRT – x formula would result in a negative number, the stop-signal was delivered at 0ms instead. Further, if the participant did not respond within 1000ms, the words "TOO SLOW" were displayed for 500ms after the Go stimulus, and participants were advised to avoid this.

2.4 Electrophysiological recording

Continuous monopolar EEG was recorded from 58 scalp sites using an elasticised cap with tin electrodes. Additional tin cup electrodes recorded activity from the left and right mastoid as well as vertical and horizontal EOG. All electrodes were referenced to an electrode on the tip of the nose, rounded midway between Fpz and Fz. Electrode impedances were below 5 k Ω . Signals were recorded DC to 200 Hz, amplified 10 times, and sampled at 1000 Hz using Neuroscan recording software and hardware (Synamps 2).

2.5 Data analysis

Due to some participants responding very quickly in the second practice block, poor inhibitory performance and very long SSRTs were displayed for the first experimental block for these participants. Therefore, behavioural analyses use only data from the last three experimental blocks, while ERP analyses use data from all four blocks.

For each participant, in addition to calculating MRT and accuracy to Go stimuli on trials where no stop signal was delivered, we calculated the probability of successfully inhibiting a response where a stop-signal was delivered (adjusted for omission errors: Tannock et al., 1995), and estimated the SSRT (Logan, 1994). The averages were calculated across blocks.

Offline, using Neuroscan software, the EEG was re-referenced to linked mastoids, bandpass filtered between 0.1 Hz (down 12 dB/octave) and 30 Hz (down 48 dB/octave, zero phase shift) and corrected for vertical eye movements and blinks (Semlitsch et al., 1986). ERPs to the stop-signal were created by epoching from 100ms before to 900ms after the onset of the stop-signal, baseline correcting to the prestimulus interval, rejecting trials with amplitude outside $\pm 100\mu\text{V}$, and separately averaging successful and failed inhibition trials. A minimum 18 trials were included in these averages; Controls had more successful inhibitions (SI) and fewer failed inhibitions (FI) than Cannabis Users (Controls SI = 59, Cannabis Users SI = 53, $F(1,92) = 3.380$, $p = 0.069$; Controls FI = 45, Cannabis Users FI = 53, $F(1,92) = 4.949$, $p = 0.029$). The N2 was detected in these waveforms as the minimum amplitude in the 200-400ms window at FCz, while the P3 was the maximum amplitude in the 350-550ms window at FCz; baseline-to-peak amplitude measurements were made at this latency at all sites to allow topographic mapping (Picton et al., 2000). Error-related ERPs were created by epoching from 500ms before to 500ms after a response, baseline correcting to the pre-response interval, rejecting trials with amplitude outside $\pm 100\mu\text{V}$, separately averaging correct and incorrect responses, and then subtracting the correct waveform from the incorrect waveform to calculate error-related response processing (e.g., Falkenstein et al., 1990). A minimum 280 correct trials, and a minimum 19 incorrect trials were included for averaging; there were no

group differences in the average number of correct trials accepted (Controls correct = 404, Cannabis Users correct = 413, $F(1,92) = 2.292$, $p = 0.134$). In contrast, and mirroring behavioural results, Cannabis Users had more incorrect trials accepted (Controls incorrect = 46, Cannabis Users incorrect = 54, $F(1,92) = 5.425$, $p = 0.022$). The ERN was detected in the difference waveform as the minimum amplitude in the 0-150ms window at FCz, and the Pe as the maximum amplitude in the window 200-450ms at CPz, and baseline-to-peak amplitude measurements were made at this latency at all sites to allow topographic mapping.

2.6 Statistical analysis

Analysis was conducted using a propensity-weighted approach. Propensity weighting involves estimating the probability of exposure, and then weighting the outcome models by the inverse of that probability. This creates a pseudo-population in which the confounders are balanced over the exposure variable (Hirano et al., 2003, Imbens, 2004).

We estimated the propensity score using a Generalized Boosted Model (GBM). GBM is a machine learning technique able to estimate the functional form of the relationship covariates and outcome with less bias than traditional approaches (McCaffrey et al., 2004). In this case, weights were estimated using the “twang” package in R 3.4.1 (R Development Core Team, 2017), controlling for the covariates: age, sex, handedness, AUDIT score, lifetime alcohol exposure, DUDIT-E score excluding cannabis, and age of onset of regular alcohol consumption. Balance between the cannabis exposed and non-exposed groups was assessed using the absolute standard difference of the weighted and unweighted samples (Ridgeway et al., 2010).

The effect of cannabis exposure was then estimated on a range of outcomes, using weighted linear regression. Models were estimated using generalised linear models for the outcomes: percentage correct responses to Go-only trials, MRT in ms to Go-only trials, SSRT in ms, amplitude of ERN at site FCz, amplitude of Pe at site CPz, latency of the ERN peak, and latency of the Pe peak. The remaining outcomes (probability of inhibition for stop-signals delivered at each delay, amplitude of N2 and P3 at site FCz, and latency of the N2 and P3 peaks) involved multiple measurements per participant, and as such were estimated using weighted generalised estimating equations to control for the lack of independence between observations. To increase robustness, all covariates from the propensity model were also included in the outcome model (Bang and Robins, 2005). Thus, statistics are based on means controlling for the effects of other covariates, some of which alter the mean considerably. This is because some of the covariates included in the propensity weighting model are strongly related to dependent variables but not cannabis use, and adjust the means substantially. For example, handedness is strongly related to Go RT (mean for left handers = 467ms; for right-handed = 515ms) but not cannabis use; when handedness is controlled for, the propensity weighted Go RT is substantially longer compared to the means in the unweighted model. For comparison with previous research, we plot unweighted means in Figures, but stress that statistics were based on the coefficients (as the difference between means in the units in which each variable was measured), and its associated standard error, provided in the text.

3. RESULTS

3.1 Demographics and balance diagnostics

Table 1 shows the characteristics of the samples before propensity weighting. Differences in alcohol consumption in particular justify the use of propensity weighting.

The weighted population showed greater balance over covariates than the unweighted population, as shown in Figure 1. However, significant imbalance remained, suggesting residual confounding by unmeasured confounders.

Table 1: Demographics of the sample for Cannabis Users and Controls (before propensity weighting).

	Cannabis Users (n = 20)		Controls (n = 74)	
	Mean	SD	Mean	SD
Sex ratio (F:M)	9:11		33:41	
Age (years)	20.3	1.2	20.0	1.2
% right-handed	85		88	
AUDIT	10.5	4.6	6.2	4.3
Lifetime standard drinks (log units)	2.9	0.4	2.1	1.0
Lifetime standard drinks (mean, CI)	822.0	528.0 – 1279.6	115.9	68.8 – 195.0
Age of onset of regular drinking	16.5	1.1	17.8	1.6
DUDIT-E score	7.2	3.0	1.3	1.7
DUDIT-E non-cannabis score [^]	3.5	2.9	0.7	1.2
Age first regular cannabis use [*]	17.2	1.2		
Frequency of cannabis use (days/month), last six months, median and range [*]	8.8	1.8-30		

[^] DUDIT-E non-cannabis use: this is a measure calculated from the frequency of use of non-cannabis drugs, and is calculated as the total DUDIT-E score minus the cannabis use frequency score.

^{*} Data not recorded for the first three participants, n = 17.

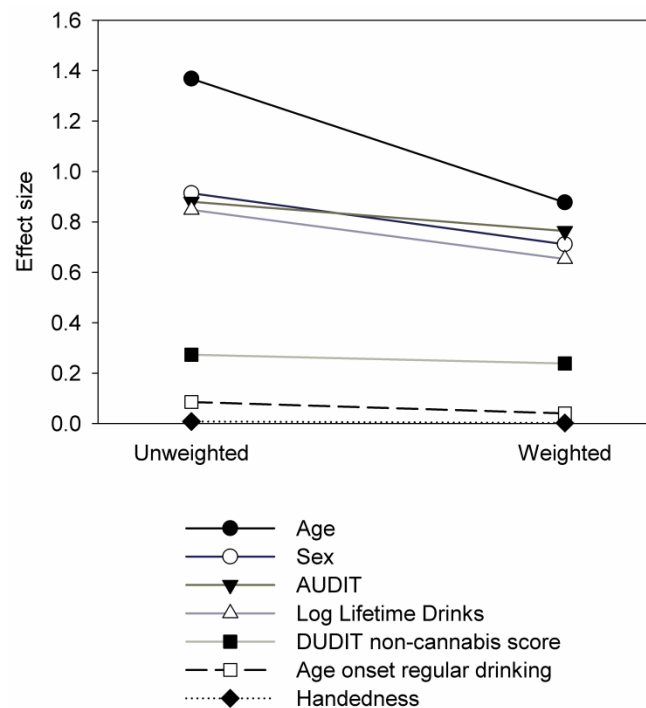


Figure 1. Absolute standard difference between groups in unweighted and propensity-weighted scores.

3.3 Behavioural performance

Figure 2 shows unweighted performance means for each group. Cannabis Users showed similar accuracy on Go trials as Controls (weighted coefficient = -0.23%, SE = 0.44, $p = 0.610$). For Go RT (right panels), despite an apparent difference between groups indicated in unweighted means, in the propensity-weighted model, Cannabis Users showed similar Go RT to Controls (weighted coefficient = 5.78ms, SE = 25.95, $p = 0.824$, bottom right panel). For Controls, the probability of inhibition was reduced for all delays relative to the MRT-450ms delay (see Figure 2, left panel, all $p < 0.001$); at the MRT-450 delay, the probability of inhibition was not significantly different between Cannabis Users and Controls in the

propensity-weighted model (coefficient = -3.08%, SE = 3.87, $p = 0.426$). Cannabis Users showed similar decreases in successful inhibition with increasing stop-signal delays (all $p \leq 0.002$). Further, SSRT was slightly but not significantly longer for Cannabis Users in the weighted model (coefficient = 4.61ms, SE = 11.33, $p = 0.685$; right panel).

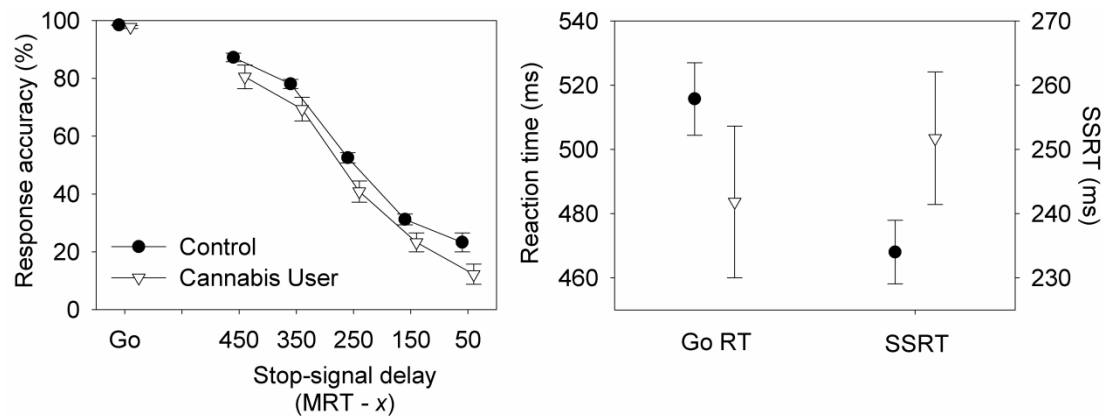


Figure 2. Left panel: unweighted mean response accuracy to Go and Stop-signal stimuli. Right panel: unweighted mean reaction time to Go stimuli, and stop-signal reaction time to stop-signal stimuli. Error bars represent standard errors.

3.4 Event-related potential data

Figures 3a and 3b show grand mean (unweighted) ERPs for each group for successful and failed inhibition trials; while Figures 3c-f show unweighted N2 and P3 amplitude and latency for each group. Figure 4 shows topographic plots of activity for each condition and group (unweighted).

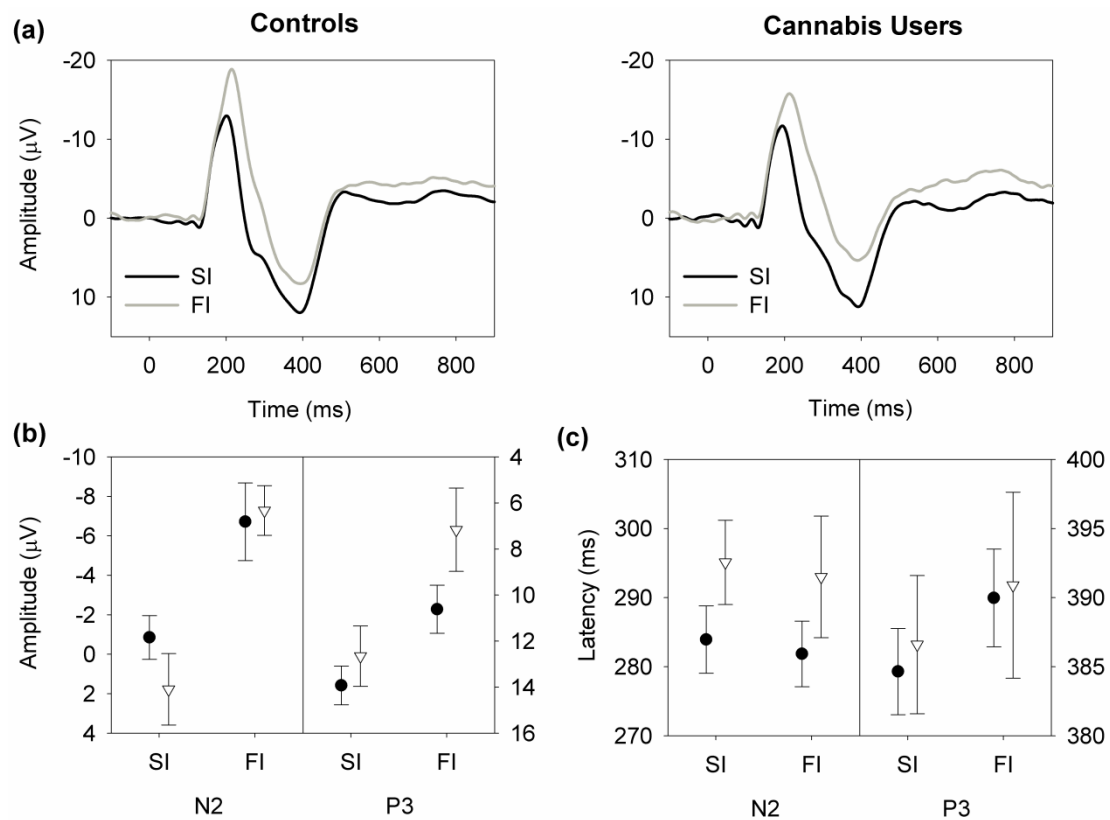


Figure 3. Grand mean unweighted ERPs for successful inhibitions (SI) and failed inhibitions (FI) at FCz, for Controls and Cannabis Users (a), and unweighted amplitude (b) and latency (c) of the N2 and P3 peaks for Controls (black circles) and Cannabis Users (white triangles). Error bars represent the standard error.

For the N2, failed inhibition was associated with a larger (more negative) N2 than successful inhibition trials in Controls (coefficient = $6.48\mu\text{V}$, SE = 0.67, $p < 0.001$; see Figure 3b). Cannabis use was associated with a larger N2 amplitude relative to Controls for failed inhibition trials (coefficient = $-4.79\mu\text{V}$, SE = 2.15, $p = 0.026$), but not successful inhibition trials (coefficient = $3.46\mu\text{V}$, SE = 2.13, $p = 0.104$).

Among controls, successful inhibition produced a larger P3 amplitude than failed inhibition (coefficient = $3.46\mu\text{V}$, SE = 0.74, $p < 0.001$; see Figure 3b). For failed inhibition trials, Cannabis Users showed a reduction in P3 amplitude relative to Controls (coefficient = $-4.57\mu\text{V}$, SE = 1.67, $p = 0.006$). For successful trials, Cannabis Users produced similar P3 amplitude compared to Controls (coefficient = $2.88\mu\text{V}$, SE = 1.56, $p = 0.064$).

Similar mean N2 latency was observed for successful and failed inhibition trials among Controls (coefficient = 3.51ms, SE = 3.69, $p = 0.342$; see Figure 3c), and for Controls and Cannabis Users for failed inhibition trials (coefficient = -2.87ms, SE = 9.88, $p = 0.771$) and successful inhibition trials (coefficient = 5.74ms, SE = 8.73, $p = 0.511$).

For P3 latency, among Controls, successful inhibition was associated with a marginally earlier P3 peak than failed inhibitions (coefficient = -5.97ms, SE = 3.19, $p = 0.061$; see Figure 3c). For both failed and successful inhibition trials, the P3 peaked slightly but not significantly later for Cannabis Users than Controls (FI trials: coefficient = 8.21ms, SE = 8.85, $p = 0.354$; SI trials: coefficient = 9.32ms, SE = 1.81, $p = 0.179$).

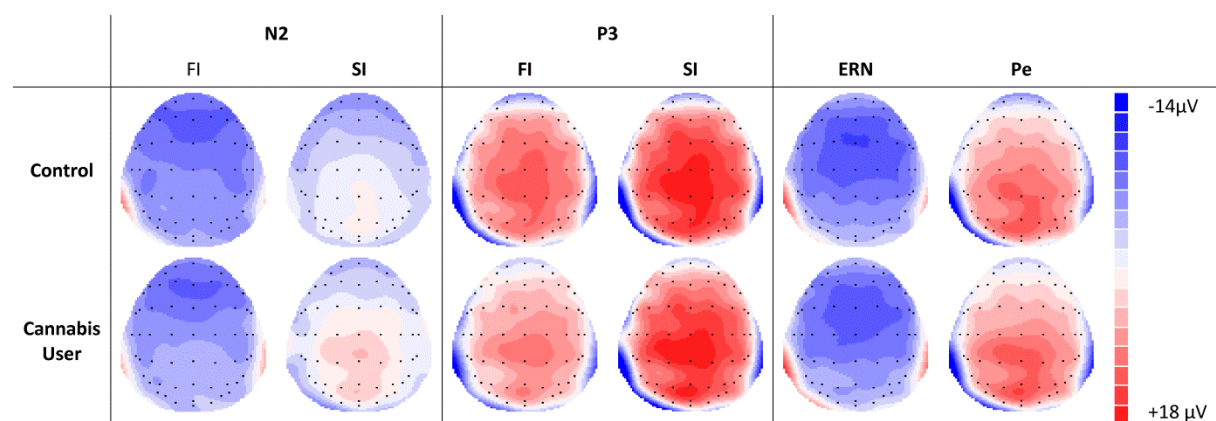


Figure 4. Topographic maps of (unweighted) activity for each component and group. All maps have the same scale (i.e., with 2 μV steps between adjacent shades).

Figure 5 shows grand mean unweighted response-locked ERPs for each group for correct and incorrect responses, and their subtraction, showing the ERN and Pe. In the propensity-weighted model, neither the amplitude of ERN nor Pe differed between groups (coefficient = $-0.78\mu\text{V}$, SE = 1.00, $p = 0.440$, and coefficient = $0.43\mu\text{V}$, SE = 1.30, $p = 0.739$, respectively), nor did the latency of ERN or Pe (coefficient = -1.07ms, SE = 8.72, $p = 0.902$, and coefficient = 25.31ms, SE = 15.78, $p = 0.112$, respectively).

4. DISCUSSION

Inhibition of inappropriate behaviours is a key aspect of executive function, and difficulties with this process have attracted growing interest as a contributor to the development and maintenance of addiction. In this study, we assessed inhibitory function in young regular recreational Cannabis Users relative to non-using Controls, after accounting for the extent of alcohol use, which is itself associated with a small deficit in inhibitory control (Smith et al., 2014). We included not only behavioural but also brain functional measures of inhibitory control and error processing, and in comparison to previous research with brain functional measures (Theunissen et al., 2012), included a broader range of components in our analysis (N2 and P3 to failed and successful inhibition trials, as well as the ERN and Pe error-related components).

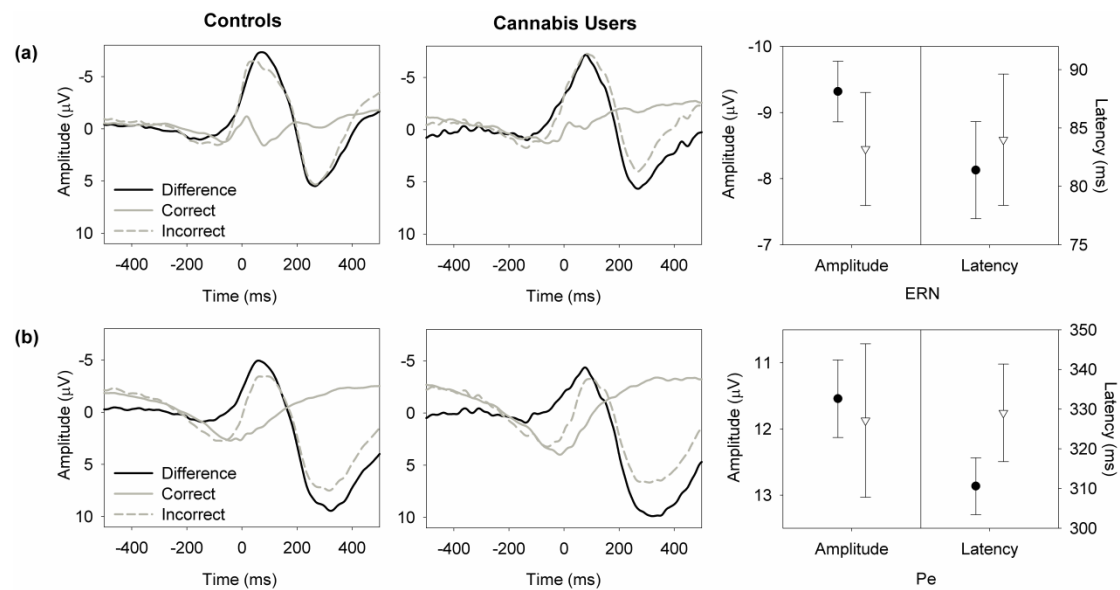


Figure 5. Left and middle: Grand mean unweighted correct, incorrect and difference (incorrect – correct) ERPs for Controls (left) and Cannabis Users (middle) at (a) FCz, at which the ERN was measured, and (b) CPz, at which the Pe was measured. Right column: mean ERN (top) and Pe (bottom) amplitude and latency for each group. Error bars represent the standard error; Controls represented by black circles, Cannabis Users by white triangles).

The young recreational cannabis user sample was generally appropriate for the research question. Although they were not particularly heavy users, they are representative of typical cannabis users of this age. The Australian Institute of Health and Welfare indicates that, among 18-29 year olds who have used cannabis in the past year, about 30% have used once a week or more, and a further 15% use approximately once a month (Australian Institute of Health and Welfare, 2011). Similarly, the cannabis user group indicated greater experimentation with other illicit drugs (as indicated by the DUDIT-E non-cannabis score); this is somewhat to be expected since illicit drug users are often polydrug users (European Monitoring Centre on Drugs and Drug Addiction, 2002, Australian Institute of Health and Welfare, 2011). However, we confirm that regular use (twice a month or more) of other drugs was an exclusion criterion. The propensity weighting approach was justified due to the substantial differences between cannabis user and non-user groups in lifetime alcohol consumption, AUDIT score, and age of onset of regular drinking; the aim of propensity weighting is balancing these confounding variables over Cannabis User and non-using Control groups (Hirano et al., 2003, Imbens, 2004).

We observed no cannabis-related difference in any behavioural response or inhibition measure: Go accuracy, Go RT, probability of inhibition and SSRT were all non-significantly different for Cannabis Users and Controls. This lack of a cannabis-related inhibitory difference is in agreement with the majority of the previously published literature (Ramaekers et al., 2009, Theunissen et al., 2012, Jutras-Aswad et al., 2012, Huddy et al., 2013, Grant et al., 2012, Filbey and Yezhuvath, 2013; but see also Moreno et al., 2012, Lovell et al., 2018), and indeed with studies of cannabis users performing a different inhibitory task (Quednow et al., 2007, Hester et al., 2009, Pope et al., 2001, Tamm et al., 2013, Tapert et al., 2007, Takagi et al., 2011, Rasmussen et al., 2016, Nicholls et al., 2015, Maij et al., 2017; but see Moreno et al., 2012).

Extending the previously published literature, we also considered a broad range of ERP components. Our significant results included larger N2 and smaller P3 amplitude for Cannabis Users relative to Controls on failed inhibition trials. These are novel results not previously reported in the literature. However, we observed no significant group differences in N2 or P3 amplitude or latency on successful inhibition trials, and no differences in N2 or P3 latency on failed inhibition trials. Our examination of the error-related ERN and Pe components also

returned no group differences. We note that the lack of error-related processing differences on failed inhibition trials has previously been reported in other inhibitory tasks using ERPs (Maij et al., 2017) and functional magnetic resonance imaging (fMRI, Hester et al., 2009). Further, our lack of group difference in successful inhibition N2 amplitude replicates Theunissen et al. (2012), and is in line with Filbey et al.'s (2013) fMRI study, where they observed no cannabis-related differences in brain activation during successful response inhibition in a stop-signal task. However, other studies examining successful inhibition in different inhibitory tasks have reported cannabis-related differences in N2 amplitude (Nicholls et al., 2015), or no difference in N2 amplitude but reduced P3 amplitude in cannabis users (Maij et al., 2017). Further, in fMRI studies, successful inhibition has been associated with increased cannabis-related activation in a range of brain regions including the anterior cingulate cortex, putamen, right inferior parietal lobe, right hippocampus and cerebellar vermis, all in the context of no difference in behavioural performance (Tapert et al., 2007, Hester et al., 2009, Rasmussen et al., 2016), typically interpreted as the greater employment of these processes to display similar behavioural performance.

It is possible that differences in results between studies are due to the type of inhibitory task employed: the "Go/NoGo" task used in those studies requires a less-urgent form of motor inhibition involving the withholding of a prepared response that has not yet been initiated – compared to the active cancellation of a motor response that has already been initiated in the stop-signal task (Wright et al., 2014, Barkley, 1997). Entangled with this are the specific trial-type comparisons typically made with each task. In the stop-signal task, brain activity is often time-locked to stop-signals and compared on trials where inhibition fails or is successful, while in the Go/NoGo task, brain activity is time-locked to Go (response execution) and NoGo (response inhibition) stimuli, and trials where inhibition is successful are simply compared with Go trials. The probability of failed inhibitions is low in the Go/NoGo task, providing too few trials for a reliable analysis.

It is unclear at this stage what is indicated by the larger N2 and reduced P3 amplitude for cannabis users, localised to failed inhibition trials, in the absence of differences in ERN and Pe. Kok et al (2004) theorised that stop-signals on such trials provide performance feedback to the participant that activates evaluative processes. Perhaps these evaluative processes are unrelated to the error-related processes elicited to the execution of an erroneous response, the latter of which do not appear to be impaired in cannabis users (Maij et al., 2017). An alternative interpretation of the N2 component in such tasks is that it reflects the detection of response conflict (e.g., Nieuwenhuis et al., 2003), whereby the presentation of a stop-signal elicits a response conflict monitoring process that causes participants to adjust performance on a trial by trial basis (van den Wildenberg et al., 2002). Greater N2 amplitude and reduced P3 amplitude by cannabis users may reflect increased efforts and/or a regulatory problem when employing this mechanism.

The limitations of the current study are that, while the propensity weighting approach had some success in balancing the groups for alcohol use, some differences remained; the alcohol variables included in our propensity weighting do not explain much variance in terms of cannabis user vs. non-user group membership, and a wider range of variables could be included in future efforts using this method. Alternately, the groups could be more carefully matched for alcohol use at the outset, possibly with recruitment of heavier users (assuming that any effects are dose-dependent), and with participants who were naïve to any other illicit drugs. Lastly, we know that acute cannabis intoxication strongly affects SSRT (Theunissen et al., 2012) and error processing (Kowal et al., 2015) but we did not assess intoxication levels either by self-report (e.g., time/date of last use) or by objective measures (e.g., saliva, blood or urine tests); future research should include these measures in order to rule out acute intoxication effects.

5. CONCLUSIONS

In summary, we found that when alcohol use is controlled as a confounding factor, cannabis users appear capable of triggering the inhibitory control process as effectively as non-users, and they do not differ in neural processes following the making of an erroneous response.

Our results have replicated the findings of previous studies, and go further to suggest previously-detected significant results in this area may have been confounded by alcohol use in participants. However, it is clear that there are some differences between cannabis users and non-users at an electrophysiological level occurring on trials when they fail to effectively inhibit a response and this warrants further investigation. The extension of our approach to the current literature, which mostly examines only behavioural indices of inhibitory control in this population group, highlights the need to focus research efforts on underlying neural processes.

6. REFERENCES

- American Psychiatric Association, 2013. *DSM-5. Diagnostic and Statistical Manual of Mental Disorders, 5th edition*, Arlington, VA, American Psychiatric Publishing.
- Australian Institute of Health and Welfare, 2011. 2010 National Drug Strategy Household Survey report. Canberra: Australian Institute of Health and Welfare.
- Band, G. P. H., Van der Molen, M. W. & Logan, G. D. 2003. Horse-race model simulations of the stop-signal procedure. *Acta Psychologica*, 112, 105-142.
- Bang, H. & Robins, J. M. 2005. Doubly robust estimation in missing data and causal inference models. *Biometrics*, 61, 962-972.
- Barkley, R. A. 1997. Behavioural inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychological Bulletin*, 121, 65-94.
- Berman, A. H., Palmstierna, T., Källmén, H. & Bergman, H. 2007. The self-report Drug Use Disorders Identification Test—Extended (DUDIT-E): Reliability, validity, and motivational index. *Journal of Substance Abuse Treatment*, 32, 357-369.
- Dimoska, A., Johnstone, S. J. & Barry, R. J. 2006. The auditory-evoked N2 and P3 components in the stop-signal task: Indices of inhibition, response-conflict or error-detection? *Brain and Cognition*, 62, 98-112.
- European Monitoring Centre for Drugs and Drug Addiction, D. 2002. *2002 Annual Report on the state of the drugs problem in the European Union and Norway*, Luxembourg, Office for Official Publications of the European Communities.
- Falkenstein, M., Hohnsbein, J., Hoormann, J. & Blanke, L. 1990. Effects of errors in choice reaction tasks on the ERP under focused and divided attention. In: BRUNIA, C. H. M., GAILLARD, A. W. K. & KOK, A. (eds.) *Psychophysiological Brain Research*. Tilburg: Tilburg University Press.
- Falkenstein, M., Hoormann, J., Christ, S. & Hohnsbein, J. 2000. ERP components on reaction errors and their functional significance: a tutorial. *Biological Psychology*, 51, 87-107.
- Filbey, F. & Yezhuvath, U. 2013. Functional connectivity in inhibitory control networks and severity of cannabis use disorder. *The American Journal of Drug and Alcohol Abuse*, 39, 382-391.
- Goldstein, R. Z. & Volkow, N. D. 2002. Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. *American Journal of Psychiatry*, 159, 1642-1652.
- Grant, J. E., Chamberlain, S. R., Schreiber, L. & Odlaug, B. L. 2012. Neuropsychological deficits associated with cannabis use in young adults. *Drug and Alcohol Dependence*, 121, 159-162.
- Hester, R., Lubman, D. I. & Yücel, M. 2010. The role of executive control in human drug addiction. In: SELF, D. W. & STALEY GOTTSCHALK, J. K. (eds.) *Behavioral Neuroscience of Drug Addiction*. Springer Berlin Heidelberg.
- Hester, R., Nestor, L. & Garavan, H. 2009. Impaired error awareness and anterior cingulate cortex hypoactivity in chronic cannabis users. *Neuropsychopharmacology*, 34, 2450-2458.
- Hirano, K., Imbens, G. & Ridder, G. 2003. Efficient estimation of average treatment effects using the estimated propensity score. *Econometrica*, 71, 1161-1189.
- Huddy, V. C., Clark, L., Harrison, I., Ron, M. A., Moutoussis, M., Barnes, T. R. E. & Joyce, E. M. 2013. Reflection impulsivity and response inhibition in first-episode psychosis: relationship to cannabis use. *Psychological Medicine*, 43, 2097-2107.
- Imbens, G. W. 2004. Nonparametric estimation of average treatment effects under exogeneity: A review. *Review of Economics and Statistics*, 86, 4-29.
- Jutras-Aswad, D., Jacobs, M. M., Yiannoukos, G., Roussos, P., Bitsios, P., Nomura, Y., Liu, X. & Hurd, Y. L. 2012. Cannabis-dependence risk relates to synergism between Neuroticism and proenkephalin SNPs associated with amygdala gene expression: Case-control study. *PLoS ONE*, 7, e39243.
- Kok, A., Ramautar, J. R., De Ruiter, M. B., Band, G. P. H. & Ridderinkhof, K. R. 2004. ERP components associated with successful and unsuccessful stopping in a stop-signal task. *Psychophysiology*, 41, 9-20.
- Kowal, M. A., van Steenbergen, H., Colzato, L. S., Hazekamp, A., van der Wee, N. J. A., Manai, M., Durieux, J. & Hommel, B. 2015. Dose-dependent effects of cannabis on

- the neural correlates of error monitoring in frequent cannabis users. *European Neuropsychopharmacology*, 25, 1943-1953.
- Logan, G. D. 1994. On the ability to inhibit thought and action: A users' guide to the stop signal paradigm. In: DAGENBACH, D. & CARR, T. H. (eds.) *Inhibitory processes in attention, memory and language*. San Diego, California: Academic Press.
- Logan, G. D., Cowan, W. B. & David, K. A. 1984. On the ability to inhibit simple and choice reaction time responses: a model and a method. *Journal of Experimental Psychology: Human Perception and Performance*, 10, 276-291.
- Lovell, M. E., Bruno, R., Johnston, J., Matthews, A., McGregor, I., Allsop, D. J. & Lintzeris, N. 2018. Cognitive, physical, and mental health outcomes between long-term cannabis and tobacco users. *Addictive Behaviors*, 79, 178-188.
- Luijten, M., Kleinjan, M. & Franken, I. H. 2016. Event-related potentials reflecting smoking cue reactivity and cognitive control as predictors of smoking relapse and resumption. *Psychopharmacology*, 233, 2857-2868.
- Mahmood, O. M., Goldenberg, D., Thayer, R., Migliorini, R., Simmons, A. N. & Tapert, S. F. 2013. Adolescents' fMRI activation to a response inhibition task predicts future substance use. *Addictive Behaviors*, 38, 1435-1441.
- Maij, D. L., Wetering, B. J. v. d. & Franken, I. H. 2017. Cognitive control in young adults with cannabis use disorder: An event-related brain potential study. *Journal of Psychopharmacology*, 31, 1015-1026.
- McCaffrey, D. F., Ridgeway, G. & Morral, A. R. 2004. Propensity score estimation with boosted regression for evaluating causal effects in observational studies. *Psychological Methods*, 9, 403-425.
- Moreno, M., Estevez, A. F., Zaldivar, F., Montes, J. M. G., Gutiérrez-Ferre, V. E., Esteban, L., Sánchez-Santed, F. & Flores, P. 2012. Impulsivity differences in recreational cannabis users and binge drinkers in a university population. *Drug and Alcohol Dependence*, 124, 355-362.
- National Health and Medical Research Council, 2009. Australian guidelines to reduce health risks from drinking alcohol. Canberra.
- Nicholls, C., Bruno, R. & Matthews, A. 2015. Chronic cannabis use and ERP correlates of visual selective attention during the performance of a flanker go/nogo task. *Biological Psychology*, 110, 115-125.
- Nieuwenhuis, S., Ridderinkhof, K. R., Blom, J., Band, G. P. H. & Kok, A. 2001. Error-related brain potentials are differentially related to awareness of response errors: Evidence from an antisaccade task. *Psychophysiology*, 38, 752-760.
- Nieuwenhuis, S., Yeung, N., van den Wildenberg, W. & Ridderinkhof, K. R. 2003. Electrophysiological correlates of anterior cingulate function in a go/no-go task: Effects of response conflict and trial type frequency. *Cognitive, Affective, & Behavioral Neuroscience*, 3, 17-26.
- Norman, A. L., Pulido, C., Squeglia, L. M., Spadoni, A. D., Paulus, M. P. & Tapert, S. F. 2011. Neural activation during inhibition predicts initiation of substance use in adolescence. *Drug and Alcohol Dependence*, 119, 216-223.
- Picton, T. W., Bentin, S., Berg, P., Donchin, E., Hillyard, S. A., Johnson, R., Miller, G. A., Ritter, W., Ruchkin, D. S., Rugg, M. D. & Taylor, M. J. 2000. Guidelines for using human event-related potentials to study cognition: Recording standards and publication criteria. *Psychophysiology*, 37, 127-152.
- Pope, H. G., Gruber, A. J., Hudson, J. I., Huestis, M. A. & Yurgelun-Todd, D. 2001. Neuropsychological performance in long-term cannabis users. *Archives of General Psychiatry*, 58, 909-915.
- Quednow, B., Kühn, K.-U., Hoppe, C., Westheide, J., Maier, W., Daum, I. & Wagner, M. 2007. Elevated impulsivity and impaired decision-making cognition in heavy users of MDMA ("Ecstasy"). *Psychopharmacology*, 189, 517-530.
- R Development Core Team, 2017. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing.
- Ramaekers, J., Kauert, G., Theunissen, E., Toennes, S. & Moeller, M. 2009. Neurocognitive performance during acute THC intoxication in heavy and occasional cannabis users. *Journal of Psychopharmacology*, 23, 266-277.
- Rasmussen, J., Casey, B. J., van Erp, T. G., Tamm, L., Epstein, J. N., Buss, C., Bjork, J. M., Molina, B. S., Velanova, K., Mathalon, D. H., Somerville, L., Swanson, J. M., Wigal,

- T., Arnold, L. E. & Potkin, S. G. 2016. ADHD and cannabis use in young adults examined using fMRI of a Go/NoGo task. *Brain Imaging Behav*, 10, 761-71.
- Ridgeway, G., McCaffrey, D. F. & Morral, A. R. 2010. Twang: Toolkit for weighting and analysis of nonequivalent groups. Version 1.2-2 ed.
- Saunders, J. B., Aasland, O. G., Babor, T. F., De La Fuente, J. R. & Grant, M. 1993. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on early detection of persons with harmful alcohol consumption-II. *Addiction*, 88, 791-804.
- Semlitsch, H. V., Anderer, P., Schuster, P. & Presslich, O. 1986. A solution for reliable and valid reduction of ocular artifact, applied to the P300 ERP. *Psychophysiology*, 23, 695-703.
- Simons, R. F. 2010. The way of our errors: Theme and variations. *Psychophysiology*, 47, 1-14.
- Skinner, H. A. 1977. *Lifetime Drinking History Structured Interview.*, Toronto, Ontario, Canada, Author.
- Smith, J. L., Iredale, J. M. & Mattick, R. P. 2016. Sex differences in the relationship between heavy alcohol use, inhibition and performance monitoring: disconnect between behavioural and brain functional measures. *Psychiatry Research: Neuroimaging*, 254, 103-111.
- Smith, J. L., Mattick, R. P., Jamadar, S. & Iredale, J. M. 2014. Deficits in behavioural inhibition in substance abuse and addiction: A meta-analysis. *Drug and Alcohol Dependence*, 145, 1-33.
- Takagi, M., Lubman, D. I., Cotton, S., Fornito, A., Baliz, Y., Tucker, A. & Yücel, M. 2011. Executive control among adolescent inhalant and cannabis users. *Drug and Alcohol Review*, 30, 629-637.
- Tamm, L., Epstein, J. N., Lisdahl, K. M., Molina, B., Tapert, S., Hinshaw, S. P., Arnold, L. E., Velanova, K., Abikoff, H. & Swanson, J. M. 2013. Impact of ADHD and cannabis use on executive functioning in young adults. *Drug and Alcohol Dependence*, 133, 607-614.
- Tannock, R., Schachar, R. & Logan, G. 1995. Methylphenidate and cognitive flexibility: Dissociated dose effects in hyperactive children. *Journal of Abnormal Child Psychology*, 23, 235-266.
- Tapert, S. F., Schweinsburg, A. D., Drummong, S. P. A., Paulus, M. P., Brown, S. A., Yang, T. T. & Frank, L. R. 2007. Functional MRI of inhibitory processing in abstinent adolescent marijuana users. *Psychopharmacology*, 194, 173-184.
- Tarter, R. E., Kirisci, L., Mezzich, A., Cornelius, J. R., Pajer, K., Vanyukov, M., Gardner, W., Blackson, T. & Clark, D. B. 2003. Neurobehavioral disinhibition in childhood predicts early age at onset of substance use disorder. *American Journal of Psychiatry*, 160, 1078-1085.
- Theunissen, E. L., Kauert, G. F., Toennes, S. W., Moeller, M. R., Sambeth, A., Blanchard, M. M. & Ramaekers, J. G. 2012. Neurophysiological functioning of occasional and heavy cannabis users during THC intoxication. *Psychopharmacology*, 220, 341-350.
- van den Wildenberg, W. P. M., van der Molen, M. W. & Logan, G. D. 2002. Reduced response readiness delays stop signal inhibition. *Acta Psychologica*, 111, 155-160.
- Wright, L., Lipszyc, J., Dupuis, A., Thayapararajah, S. W. & Schachar, R. 2014. Response Inhibition and Psychopathology: A Meta-Analysis of Go/No-Go Task Performance. *Journal of Abnormal Psychology*, 123, 429-439.

ACKNOWLEDGEMENTS

This study was funded by a UNSW Vice-Chancellor's Postdoctoral Fellowship to Dr Smith. The National Drug and Alcohol Research Centre at the University of New South Wales is supported by funding from the Australian Government under the Substance Misuse Prevention and Service Improvements Grants Fund.

Thanks are due to Mr Tony Kemp for writing the stimulus presentation program.